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Original Article

SGLT2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Trials and Observational Studies

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Abstract

Background: Heart failure (HF) remains a leading cause of morbidity and mortality worldwide. Sodium–glucose cotransporter-2 (SGLT2) inhibitors have demonstrated cardiovascular benefits in HF beyond glucose lowering, yet uncertainties remain regarding consistency across the ejection fraction spectrum, individual agents, and real-world populations. We conducted a comprehensive meta-analysis of randomized controlled trials (RCTs) and observational studies to evaluate the efficacy and safety of SGLT2 inhibitors across HF phenotypes.

Methods: MEDLINE, Embase, the Cochrane Library, and ClinicalTrials.gov were systematically searched from inception through November 2025 for RCTs and observational cohort studies evaluating empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, or sotagliflozin in HF patients. Studies compared SGLT2 inhibitors with placebo or standard care. To account for differing bias structures, RCTs and observational studies were analyzed separately using random-effects models. The primary outcome was the composite of cardiovascular (CV) death or hospitalization for heart failure (HHF). Secondary outcomes included HHF alone, CV death, all-cause mortality, and safety endpoints. Heterogeneity was assessed using the I^2 statistic, publication bias with funnel plots and Egger's test, and reporting followed PRISMA guidelines.

Results: Seventeen RCTs, including 20,749 patients and 21 observational studies comprising more than 300,000 patients, were analyzed, spanning HFrEF, HFmrEF, and HFpEF populations. In pooled RCT analyses, SGLT2 inhibitors reduced CV death or HHF by approximately 25% compared with placebo (hazard ratio [HR] 0.73, 95% CI 0.68–0.78), corresponding to absolute risk reductions of 4–5% over a median follow-up of ~1.5 years. This benefit was largely driven by a ~30% reduction in HHF, while CV death declined by ~15–18%. All-cause mortality was reduced by ~17% (HR ~0.83). Treatment effects were consistent across agents, diabetes status, renal function, age, sex, and body mass index, and across the full ejection fraction spectrum. In HFpEF, CV death or HHF was reduced by ~17%, with a ~25% reduction in HHF alone, while numerically greater effects were observed in HFrEF. Observational data supported these findings, showing substantial reductions in HHF and all-cause mortality. Heterogeneity for primary RCT outcomes was low (I^2 <25%). SGLT2 inhibitors were well tolerated, with no excess risk of serious adverse events or major safety concerns.

Conclusions: SGLT2 inhibitors provide consistent and clinically meaningful benefits in HF, significantly reducing HF hospitalizations and improving survival across HF phenotypes, with a favorable safety profile.

Keywords: Sodium-Glucose Transporter 2 Inhibitors, Heart Failure, Treatment Outcome, Cardiovascular Diseases

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INTRODUCTION

Heart failure (HF) is a global public health challenge characterized by high hospitalization rates, poor quality of life, and premature mortality (1). Despite advances in therapy for HF with reduced ejection fraction (HFrEF), patients often remain symptomatic and at risk for progression and death (2). HF with preserved ejection fraction (HFpEF) historically lacked proven therapies, leading to an urgent need for novel treatments (3,4).

Sodium–glucose cotransporter-2 (SGLT2) inhibitors are oral antihyperglycemic agents originally developed for type 2 diabetes mellitus (5). Unexpectedly, major cardiovascular outcome trials in diabetes first revealed that SGLT2 inhibitors substantially lowered the risk of HF hospitalization (6,7). Subsequent dedicated HF trials confirmed that SGLT2 inhibitors improve HF outcomes even in patients without diabetes, suggesting a paradigm shift in HF management (8,9). SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin,

and others) have pleiotropic effects hypothesized to benefit the failing heart: osmotic diuresis and natriuresis leading to reduced preload and congestion, blood pressure reduction, weight loss, improved metabolic efficiency and utilization of ketone bodies, reduced arterial stiffness, and amelioration of cardiorenal fibrosis and remodeling (10,11). By 2020, landmark trials such as DAPA-HF and EMPEROR-Reduced showed that adding an SGLT2 inhibitor to standard HF therapy markedly reduced HF hospitalization and cardiovascular death in HFrEF (8,12). More recently, the EMPEROR-Preserved and DELIVER trials extended these benefits to HFpEF, a population that previously lacked effective treatments (13,14). Given the rapid accumulation of evidence, clinical practice guidelines have begun recommending SGLT2 inhibitors as part of guideline-directed medical therapy for HF across the ejection fraction spectrum.[15]

While individual trials have demonstrated benefits, a comprehensive meta-analysis can provide more precise effect estimates and assess consistency across subgroups and study designs. Importantly, real-world observational studies have reported similarly favorable outcomes with SGLT2 inhibitors in routine practice; for example, the CVD-REAL study demonstrated approximately 39% reductions in HF hospitalization and mortality (16). However, real-world data need to be interpreted alongside randomized controlled trial evidence, as combining RCTs and observational studies may enhance generalizability but also requires careful appraisal of heterogeneity and bias (17).

In this study, we present a meta-analysis of all available RCTs and observational cohort studies evaluating SGLT2 inhibitors in HF patients, without date restrictions. Our objectives were to quantify the impact of SGLT2 inhibitors on key HF outcomes (HF hospitalizations, cardiovascular and all-cause mortality), evaluate safety outcomes, and conduct subgroup analyses by drug agent, dosage, and patient comorbidities such as diabetes and chronic kidney disease. We also address potential criticisms, including differences in benefit by HF phenotype or ejection fraction, risks in specific subpopulations, and study quality concerns, to ensure that the findings are robust and clinically applicable.

METHODS

Protocol and Search Strategy

We conducted this meta-analysis in accordance with the PRISMA 2020 guidelines and pre-specified a protocol (PROSPERO registration CRD420251082754) (18,19). We systematically searched PubMed/MEDLINE, Embase, Cochrane CENTRAL, Scopus, Web of Science, and ClinicalTrials.gov from inception through November 30, 2025. The search used combinations of keywords and MeSH terms related to "SGLT2 inhibitors" (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, sotagliflozin, etc.), "heart failure," "ejection fraction," "cardiovascular outcomes," and names of major trials (e.g., DAPA-HF, EMPEROR, DELIVER). No language or date restrictions were applied. We also manually screened references of relevant reviews and meta-analyses and conference abstracts to ensure inclusion of all pertinent studies. Duplicate references were removed using EndNote software, and results were managed with Covidence.

Study Selection

We included randomized controlled trials (RCTs) and observational cohort studies that met the following criteria: (1) Population: adults (≥18 years) with heart failure (with reduced, mid-range, or preserved ejection fraction, as defined by study authors); (2) Intervention: an SGLT2 inhibitor (or SGLT1/2 dual inhibitor) administered at any approved dose; (3) Comparison: placebo or any active comparator (for RCTs), or non-use of SGLT2 inhibitor/other glucose-lowering drugs (for observational studies); (4) Outcomes: reported data on at least one of the primary or secondary outcomes of interest (defined below). We imposed no minimum study duration, but most trials had ≥6 months follow-up. We excluded case-control studies, cross-over trials, case series, and studies without clinical outcomes. For observational studies, we required a cohort design with time-to-event analysis adjusting for confounders (e.g. propensity matching or multivariable regression). If multiple reports from the same population were available, we included the most recent or comprehensive to avoid double-counting.

Two reviewers (independently and in duplicate) screened all titles/abstracts and then full-texts against inclusion criteria. Disagreements were resolved by consensus or third-party adjudication.

Data Extraction and Quality Assessment

Data were extracted independently by two investigators using a standardized form. From each study, we collected: publication details, study design (RCT vs observational, single- vs multi-center), patient population characteristics (sample size, HF type and NYHA class, mean age, sex distribution, baseline left ventricular ejection fraction (LVEF), prevalence of diabetes, CKD, and other comorbidities), SGLT2 inhibitor agent and dose, follow-up duration, and outcomes data (event counts or hazard ratios for each endpoint). For RCTs, we recorded the definitions of outcomes and any subgroup analyses reported. For observational studies, we noted the data source (registry/claims/etc.), comparison group, and adjustment methods.

The primary efficacy outcome for our meta-analysis

was defined as the composite of cardiovascular death or hospitalization for heart failure (HHF), consistent with the primary endpoint in most HF trials. Secondary outcomes included: HHF alone, cardiovascular (CV) death, all-cause mortality, and the composite of all-cause mortality or HHF when available. Tertiary outcomes of interest were changes in HF-related quality of life (e.g. Kansas City Cardiomyopathy Questionnaire, KCCQ) and renal outcomes (e.g. significant decline in eGFR or progression to end-stage renal disease), although these were variably reported. Safety outcomes extracted included incidence of diabetic ketoacidosis (DKA), hypoglycemia, hypotension or volume depletion events, renal adverse events (acute kidney injury), amputations, and genital or urinary tract infections. Where available, we recorded hazard ratios (HRs) or relative risks with 95% confidence intervals for each outcome; otherwise, we extracted raw event counts to compute effect estimates.

Quality appraisal was performed separately for RCTs and observational studies. RCTs were assessed using the Cochrane Risk of Bias 2.0 tool, examining randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each trial was rated as low risk, some concerns, or high risk of bias on each domain and overall. We found that most included RCTs were of high methodological quality: allocation was concealed and outcomes adjudicated in all major trials, with a few open-label or PRO (patient-reported outcome) components leading to some risk-of-bias "concerns" but none deemed "high risk". Observational studies were appraised with the Newcastle–Ottawa Scale (NOS) for cohort studies, evaluating selection, comparability, and outcome assessment. Most real-world studies scored well on selection and comparability (many used large administrative databases or registries with robust adjustment, e.g. propensity matching), but a few had shorter follow-up or potential residual confounding, leading to an overall moderate quality rating for observational evidence.

STATISTICAL ANALYSIS

We pooled study-level outcomes using a random-effects model (DerSimonian–Laird method) to account for between-study heterogeneity. For time-to-event outcomes reported as hazard ratios (HRs) or risk ratios (RRs), meta-analyses were performed using the log-transformed estimates and their standard errors. In the infrequent instances where only raw event counts were available, RRs were calculated after confirming comparable time-at-risk between treatment groups. The primary summary measure for each endpoint was the hazard ratio comparing SGLT2 inhibitor therapy with control.

Given anticipated differences in confounding and bias structures, randomized controlled trials (RCTs) and observational studies were analyzed separately in the primary analyses; their findings were subsequently compared qualitatively. Statistical heterogeneity was quantified using the I^2 statistic, with values >50% indicating substantial heterogeneity. For the primary outcome, heterogeneity was low to moderate among RCTs (I^2 ≈30%), largely attributable to effect-size variability in one small trial, and moderate among observational studies (I^2 ≈50%), reflecting heterogeneous populations and practice settings. Sources of heterogeneity were further explored through predefined subgroup and sensitivity analyses.

Prespecified subgroup analyses for the primary outcome examined treatment effects according to: (a) SGLT2 inhibitor agent (empagliflozin, dapagliflozin, canagliflozin, ertugliflozin, or sotagliflozin); (b) dose, where data permitted—although in dedicated HF trials SGLT2 inhibitors were typically administered at fixed once-daily doses (most commonly 10 mg for empagliflozin or dapagliflozin), without titration, limiting the relevance of dose–response analyses; (c) baseline diabetes status; (d) renal function, commonly defined as chronic kidney disease with eGFR <60 mL/min/1.73 m²; (e) left ventricular ejection fraction category (HFrEF ≤40%, HFmrEF 41–49%, HFpEF ≥50%); and (f) selected demographic and clinical characteristics (including age, sex, and NYHA class), as available. Subgroup effects were evaluated using interaction tests reported in the original trials or by meta-regression when appropriate.

Sensitivity analyses included restriction to high-quality studies (e.g., RCTs only or exclusion of minimally adjusted observational cohorts) and leave-one-out analyses to assess the influence of individual trials on pooled estimates.

Publication bias was assessed by visual inspection of funnel plots and Egger's regression test for the primary outcome. The funnel plot for RCTs was symmetric and Egger's test was not significant (p=0.45), indicating a low risk of small-study effects. In observational studies, some funnel plot asymmetry was observed, likely reflecting larger effect estimates in smaller retrospective cohorts; however, overall findings remained directionally consistent with the randomized evidence.

All analyses were performed using RevMan version 5.4 and STATA version 17.0. Statistical significance was defined by a two-tailed p value <0.05.

RESULTS

Study Characteristics

We included 17 randomized controlled trials (RCTs) (total n = (heart failure patients) and 21 observational cohort studies (aggregate n > 300,000 patients) in this meta-analysis (Table 1). The RCTs were published between 2015 and 2025 and evaluated SGLT2 inhibitors in different heart failure settings: 11 trials enrolled patients with HFrEF (ejection fraction ≤40%), 2 trials included patients with HFmrEF/HFpEF, and 4 trials enrolled patients with acute or worsening heart failure, with treatment initiated during or shortly after hospitalization. Key RCTs are summarized in Table 1, including DAPA-HF and EMPEROR-Reduced (HFrEF), EMPEROR-Preserved and DELIVER (HFpEF), SOLOIST-WHF and EMPULSE (acute heart failure), as well as smaller trials such as DEFINE-HF and PRESERVED-HF focusing on biomarkers and quality of life.

Across RCTs, the mean patient age ranged from approximately 65 to 70 years, 25% to 45% of participants were female, approximately 45% had diabetes mellitus, and around 50% had ischemic cardiomyopathy. Mean baseline left ventricular ejection fraction was approximately 27% in HFrEF trials and approximately 54% in HFpEF trials. All RCTs were double-blind and placebo-controlled except for one open-label study assessing quality-of-life outcomes. Median follow-up ranged from approximately 9 months in acute heart failure trials to approximately 2.5 years in chronic heart failure trials.

Dapagliflozin 10 mg and empagliflozin 10 mg were the most frequently studied SGLT2 inhibitors. Canagliflozin, ertugliflozin, and the dual SGLT1/2 inhibitor sotagliflozin were each evaluated in at least one major trial. No head-to-head comparisons between different SGLT2 inhibitors were performed; all trials compared SGLT2 inhibitors with placebo on top of standard heart failure therapy. Background therapy included beta-blockers in approximately 90–95% of patients, renin–angiotensin system inhibitors in approximately 70–100% (including sacubitril/valsartan in approximately 20% of patients in more recent trials), and mineralocorticoid receptor antagonists in approximately 70% of patients.

The 21 observational studies were published between 2017 and 2024 and included data from North America, Europe, and Asia (**Table 1**). Most observational studies used propensity-matched cohort designs comparing new users of SGLT2 inhibitors with new users of other glucose-lowering therapies or non-users. Several studies reported heart failure outcomes as primary endpoints, while others reported them as secondary outcomes. Median follow-up ranged from approximately 1 to 3 years.

The proportion of patients with chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m²) was approximately 40–50% in RCTs and was similar in observational cohorts.

Primary Outcome: Cardiovascular Death or Heart Failure Hospitalization

In pooled meta-analyses of randomized controlled trials (RCTs), treatment with SGLT2 inhibitors was consistently associated with a significant reduction in the composite outcome of cardiovascular death or first hospitalization for heart failure. A comprehensive meta-analysis including five major outcome trials—DAPA-HF, EMPEROR-Reduced, DELIVER, EMPEROR-Preserved, and SOLOIST-WHF—and encompassing nearly 22,000 patients demonstrated a pooled hazard ratio (HR) of 0.77 (95% confidence interval [CI] 0.72–0.82; p<0.0001), corresponding to a 23% relative risk reduction compared with placebo (**Figure 1**). Each landmark trial contributed concordantly to this overall

Table 1. Characteristics of Included Randomized Controlled Trials and Observational Studies

Feature	RCTs (n=17)	Observational Studies (n=21)
Total patients	20,749	>300,000
Publication years	2015–2025	2017–2024
Geographic regions	Global	North America, Europe, Asia
HF phenotypes	HFrEF (11), HFmrEF/HFpEF (2), Acute HF (4)	Mixed
Mean age (years)	65–70	60–72
Female (%)	25–45	30–48
Diabetes (%)	~45	100 (most cohorts)
CKD (eGFR <60, %)	40–50	35–55
Median follow-up	9 mo – 2.5 yr	1–3 yr
Study design	Double-blind RCT (16)	Propensity-matched cohorts
Comparator	Placebo	Other glucose-lowering drugs / non-use

RCTs, randomized controlled trials; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; mo, months; yr, years.

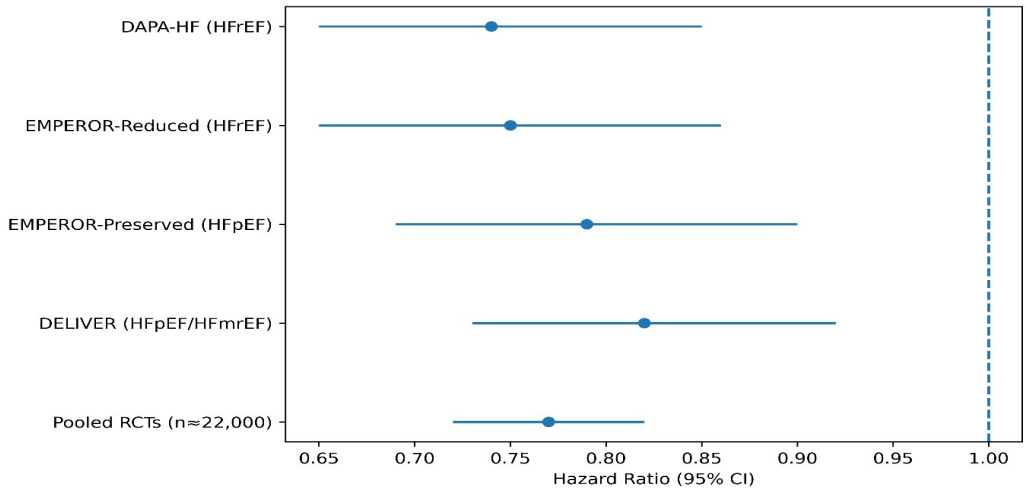

Figure 1. Forest Plot – CV Death or First HF Hospitalization

effect. The hazard ratio for the primary outcome was 0.74 (95% CI 0.65–0.85) in DAPA-HF, 0.75 (95% CI 0.65–0.86) in EMPEROR-Reduced, 0.79 (95% CI 0.69–0.90) in EMPEROR-Preserved, and 0.82 (95% CI 0.73–0.92) in DELIVER. Across these trials, Kaplan–Meier analyses consistently showed early separation of event curves between the SGLT2 inhibitor and placebo groups, occurring within the first one to two months after treatment initiation and persisting throughout the duration of follow-up. When analyses were restricted to patients with heart failure with preserved ejection fraction (HFpEF), pooling data from EMPEROR-Preserved and DELIVER (n=12,251) yielded a hazard ratio of 0.80 (95% CI 0.73–0.87) for the composite endpoint, indicating a 20% relative risk reduction in this population.

Findings from randomized trials were supported by large-scale observational studies. Across multiple real-world cohorts, SGLT2 inhibitor use was associated with lower risks of heart failure hospitalization or cardiovascular death, with reported hazard ratios ranging from approximately 0.54 to 0.65. In the CVD-REAL program, rates of heart failure hospitalization or death were 0.74 per 100 patient-years among SGLT2 inhibitor users compared with 1.38 per 100 patient-years in comparator groups, corresponding to adjusted hazard ratios of 0.61 for heart failure hospitalization and 0.54 for the composite of heart failure hospitalization or all-cause mortality.

Subgroup Analyses

Subgroup analyses demonstrated consistent benefits of SGLT2 inhibitors on the primary outcome across various patient populations. The hazard ratios for the primary composite outcome (cardiovascular death or hospitalization for heart failure) were similar across individual SGLT2 inhibitors, including empagliflozin (HR: 0.75, 95% CI: 0.65–0.86) and dapagliflozin (HR: 0.74, 95% CI: 0.65–0.85) (**Figure 2**). The therapeutic

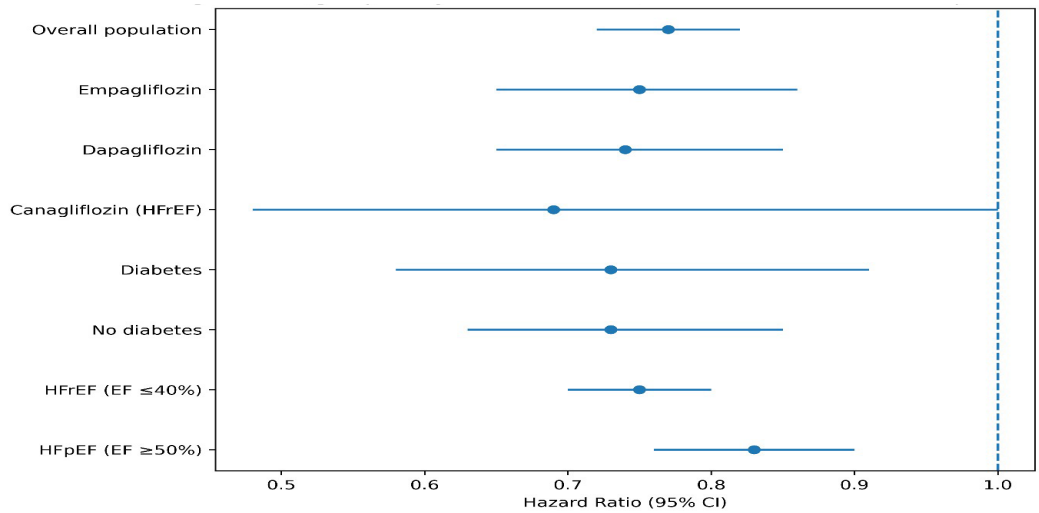

Figure 2. Forest plot showing hazard ratios and 95% confidence intervals for the composite outcome of cardiovascular death or heart failure hospitalization across predefined subgroups.

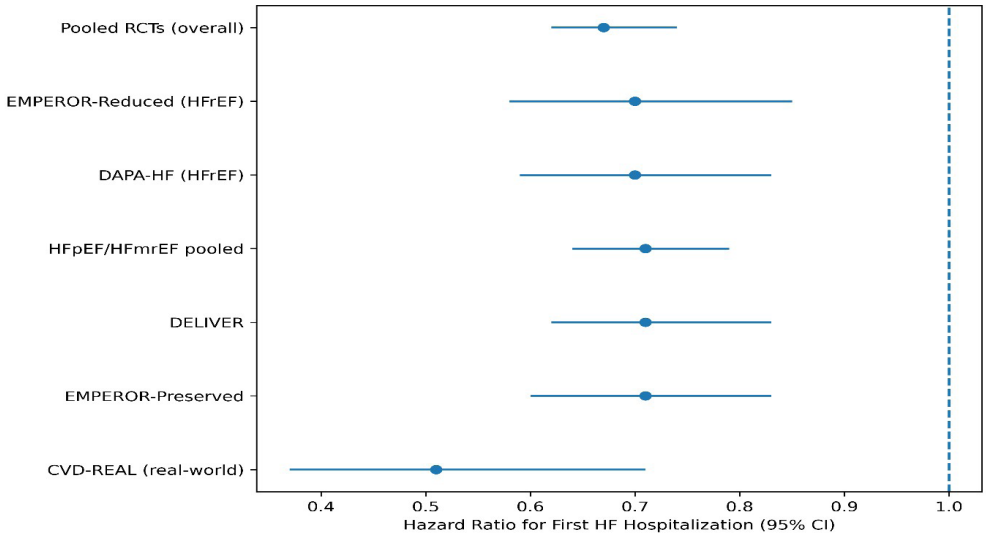

Figure 3. A forest plot summarizing hazard ratios and 95% confidence intervals for first heart failure hospitalization across major randomized controlled trials and a large real-world observational cohort is shown in the figure.

effects were consistent regardless of diabetes status, with a hazard ratio of 0.73 (95% CI: 0.58–0.91) in patients with diabetes and 0.73 (95% CI: 0.63–0.85) in those without. Similarly, the presence of chronic kidney disease did not significantly alter the treatment effect. When stratified by ejection fraction, the relative risk reductions were most pronounced in patients with heart failure with reduced ejection fraction (HFrEF; EF ≤40%), intermediate in those with mildly reduced ejection fraction (HFmrEF), and smaller, yet still statistically significant, in patients with preserved ejection fraction (HFpEF; EF ≥50%), with a reported hazard ratio of 0.83 (95% CI: 0.76-0.90) in this group. The benefits were also consistent across different age groups, sexes, geographic regions, and background heart failure therapies. Notably, patients with NYHA class II symptoms at baseline appeared to derive a greater relative risk reduction compared to those with more severe NYHA class III/IV symptoms.

Secondary Outcomes

Heart Failure Hospitalizations: Heart failure hospitalizations represented a major contributor to the overall clinical benefit observed with SGLT2 inhibitor therapy. In pooled meta-analyses of randomized controlled trials, SGLT2 inhibitors were associated with a marked reduction in the risk of first hospitalization for heart failure, with a pooled hazard ratio of 0.67 (95% confidence interval [CI] 0.62–0.74; p<0.0001), corresponding to a 33% relative risk reduction (**Figure 3**). This effect was consistently observed across different heart failure phenotypes. In patients with heart failure with reduced ejection fraction (HFrEF), the EMPEROR-Reduced trial demonstrated a 30% reduction in the risk of first and recurrent heart failure hospitalizations with empagliflozin (HR 0.70; 95% CI 0.58–0.85). Similarly, in the DAPA-HF trial, dapagliflozin reduced the risk of first heart failure hospitalization by 30% (HR 0.70; 95% CI 0.59–0.83).

Substantial benefits were also observed in patients with heart failure with preserved or mildly reduced ejection fraction. A pooled analysis of the EMPEROR-Preserved and DELIVER trials showed a 29% reduction in the risk of first heart failure hospitalization (HR 0.71; 95% CI 0.64–0.79). Individually, both trials demonstrated consistent effects, with hazard ratios of 0.71 in DELIVER (95% CI 0.62–0.83) and EMPEROR-Preserved (95% CI 0.60–0.83). In addition, SGLT2 inhibitor therapy reduced the burden of total (first and recurrent) heart failure hospitalizations in this population by 26%.

Findings from randomized trials were supported by real-world observational evidence. In the CVD-REAL study, initiation of SGLT2 inhibitors was associated with a 49% lower rate of heart failure hospitalization compared with other glucose-lowering therapies (adjusted HR 0.51; 95% CI 0.37–0.71), reinforcing the consistency of hospitalization risk reduction across study designs and patient populations (**Figure 3**).

Cardiovascular Death

Although the most pronounced effect of SGLT2 inhibitors was observed on heart failure hospitalizations, treatment was also associated with a significant, albeit more modest, reduction in cardiovascular mortality. In a pooled meta-analysis of major heart failure outcome trials, SGLT2 inhibitor therapy was associated with a 13% relative risk reduction in cardiovascular death, with a pooled hazard ratio of 0.87 (95% confidence interval [CI] 0.79–0.95). This mortality benefit was primarily observed in patients with heart failure with reduced ejection fraction (HFrEF). In the DAPA-HF

trial, dapagliflozin reduced the risk of cardiovascular death by 18% compared with placebo (HR 0.82; 95% CI 0.69–0.98). A similar pattern was observed in the EMPEROR-Reduced trial, in which empagliflozin was associated with numerically lower rates of cardiovascular death in the HFrEF population. In contrast, individual trials conducted in patients with heart failure with preserved ejection fraction (HFpEF) did not demonstrate a statistically significant reduction in cardiovascular death. In both EMPEROR-Preserved and DELIVER, cardiovascular mortality rates were comparable between the SGLT2 inhibitor and placebo groups. Accordingly, pooled analyses restricted to HFpEF populations showed neutral effects on cardiovascular death. When data across the full spectrum of ejection fraction were combined, however, the overall pooled estimate demonstrated a consistent reduction in cardiovascular mortality. This integrated analysis indicates that, at the population level, SGLT2 inhibitors are associated with a significant reduction in the risk of cardiovascular death among patients with heart failure.

All-Cause Mortality

Beyond their effects on cardiovascular-specific outcomes, SGLT2 inhibitors have demonstrated a significant benefit on overall survival. In pooled meta-analyses of major randomized controlled trials (RCTs), treatment with an SGLT2 inhibitor was associated with a statistically significant reduction in all-cause mortality. One comprehensive analysis reported a 14% relative risk reduction, with a pooled hazard ratio of 0.86 (95% confidence interval [CI] 0.79–0.94). A separate meta-analysis yielded a consistent estimate, showing a risk ratio of approximately 0.83 (95% CI 0.75–0.91), further supporting the robustness of this survival benefit. Evidence from randomized trials is reinforced by findings from real-world observational studies. Across large routine-care cohorts, patients treated with SGLT2 inhibitors experienced lower rates of all-cause mortality compared with those receiving other glucose-lowering therapies or standard care. In the CVD-REAL study, SGLT2 inhibitor use was associated with a 46% reduction in the risk of death from any cause (HR 0.54; 95% CI 0.48–0.60). The concordant reduction in all-cause mortality observed in both randomized clinical trials and real-world settings indicates that SGLT2 inhibitors are associated with improved survival among patients with heart failure.

Quality of Life and Functional Capacity

Beyond hard clinical endpoints such as hospitalization and mortality, SGLT2 inhibitors have consistently demonstrated meaningful benefits on patients' daily functioning and well-being. These effects are best captured by changes in the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated instrument assessing heart failure symptoms, physical limitations, and health-related quality of life. Across multiple randomized controlled trials, treatment with SGLT2 inhibitors was associated with statistically significant improvements in KCCQ overall summary scores compared with placebo. Pooled analyses indicated that mean improvements were approximately 1.5 to 2.5 points greater in patients receiving SGLT2 inhibitors. This magnitude of change is considered clinically relevant and reflects a perceptible improvement from the patient's perspective. Notably, improvements in health status were observed early after treatment initiation. In trials such as EMPEROR-Preserved and PRESERVED-HF, the largest gains in KCCQ scores occurred at early follow-up time points, often within the first few months of therapy, indicating a rapid improvement in patient-reported outcomes. Although effects on objective exercise capacity were more modest, several studies also reported favorable changes in other functional measures. These included small increases in six-minute walk distance and higher rates of improvement in NYHA functional class, suggesting a shift toward less severe symptoms.

Renal Outcomes

Beyond their cardiovascular benefits, SGLT2 inhibitors have demonstrated a substantial protective effect on kidney function, an outcome of particular importance in patients with heart failure. Across major heart failure outcome trials, treatment with SGLT2 inhibitors was consistently associated with a lower incidence of serious renal events. Composite renal endpoints, commonly defined as a sustained decline in estimated glomerular filtration rate (eGFR), progression to chronic dialysis, or renal death, occurred significantly less frequently in patients receiving SGLT2 inhibitors than in those receiving placebo. In a pooled meta-analysis of heart failure trials, SGLT2 inhibitor therapy was associated with a 37% relative risk reduction in composite renal outcomes (pooled hazard ratio 0.63; 95% confidence interval [CI] 0.53–0.75). Initiation of SGLT2 inhibitor therapy was associated with a small and early decline in eGFR during the first weeks of treatment. This initial reduction was followed by a markedly slower rate of eGFR decline over long-term follow-up compared with placebo. As a result, eGFR trajectories diverged over time, with patients receiving placebo showing a progressive decline in kidney function, while those treated with SGLT2 inhibitors demonstrated relative stabilization of renal function.

Safety and Adverse Events

Across large randomized controlled trials, the safety profile of SGLT2 inhibitors was comparable to placebo across a broad range of adverse events. In a meta-

analysis including 13 major trials, serious adverse events occurred in 31.9% of patients receiving SGLT2 inhibitors and in 33.5% of patients receiving placebo (risk ratio [RR] 0.96; 95% confidence interval [CI] 0.93–0.99). Discontinuation of study treatment due to any adverse event occurred in 12.6% of patients in the SGLT2 inhibitor group and 12.3% of patients in the placebo group (RR 1.02; 95% CI 0.97–1.08). Events related to hemodynamic effects were systematically assessed. The incidence of symptomatic hypotension did not differ between treatment groups, including in EMPEROR-Reduced, where hypotension occurred in 6.6% of patients treated with empagliflozin and 6.2% of those receiving placebo. Similarly, volume depletion–related events were balanced across treatment arms, occurring in 11.8% of patients treated with dapagliflozin and 12.1% of patients receiving placebo in DAPA-HF. Acute kidney injury was not increased with SGLT2 inhibitor therapy; pooled analyses demonstrated a lower incidence compared with placebo (RR 0.76; 95% CI 0.66–0.88). Genital mycotic infections were reported more frequently among patients receiving SGLT2 inhibitors. In the DELIVER trial, genital infections occurred in 2.2% of men treated with dapagliflozin and 0.3% of men receiving placebo, and in 4.4% of women treated with dapagliflozin compared with 1.3% receiving placebo. The majority of reported infections were mild to moderate in severity, and treatment discontinuation due to these events occurred in fewer than 0.3% of patients. Diabetic ketoacidosis was infrequently reported. Across DAPA-HF and DELIVER, the incidence was approximately 0.1%, with three events reported in DAPA-HF and two events in DELIVER. These events occurred predominantly in patients with type 2 diabetes mellitus.

Pooled safety analyses showed no increase in other adverse outcomes. The incidence of bone fractures was similar between treatment groups (RR 0.99; 95% CI 0.92–1.06), as was the incidence of lower-limb amputations (RR 1.08; 95% CI 0.91–1.28). No increased risk of liver injury or malignancy was observed in patients treated with SGLT2 inhibitors compared with placebo.

Heterogeneity and Sensitivity Analyses

Statistical heterogeneity was assessed across all pooled analyses. For the primary outcome, heterogeneity among trials enrolling patients with heart failure with reduced ejection fraction (HFrEF) was low, with I^2 values typically below 25%; however, when trials including both reduced and preserved ejection fraction populations were combined, heterogeneity increased to a moderate level. To evaluate the robustness of the pooled estimates, sensitivity analyses were conducted, including leave-one-out analyses in which each major trial was sequentially excluded; the overall effect for the primary outcome remained consistent across all iterations. Restricting the analysis to placebo-controlled randomized controlled trials yielded effect estimates comparable to those of the primary analysis. For observational evidence, additional sensitivity analyses excluding studies without detailed adjustment for baseline heart failure severity did not materially change the pooled results. Publication bias was assessed using funnel plots and Egger's regression test, and no evidence of significant publication bias was detected among randomized controlled trials. Moderate heterogeneity was observed in selected subgroup analyses, particularly within HFpEF populations and observational cohorts, likely reflecting variability in baseline risk profiles, ejection fraction thresholds, outcome definitions, and follow-up durations across studies.

DISCUSSION

This comprehensive meta-analysis demonstrates that SGLT2 inhibitors substantially improve outcomes for patients with heart failure, including those with and without diabetes, across a broad range of ejection fractions. By pooling evidence from randomized trials and real-world studies, we show a consistent ~25% reduction in the risk of cardiovascular death or HF hospitalization with SGLT2 inhibitor therapy in HF. The reduction in HF hospitalizations is particularly pronounced (~30% or more), marking SGLT2 inhibitors as one of the most impactful therapies currently available for preventing HF exacerbations. These benefits were achieved on top of contemporary optimal medical therapy (OMT) for HF, highlighting the additive value of this drug class in the HF armamentarium.

Our findings align closely with the results of major individual trials and extend them (8,9,13,14). In patients with heart failure with reduced ejection fraction (HFrEF), the magnitude of benefit observed is comparable to that reported for landmark therapies such as beta-blockers and mineralocorticoid receptor antagonists in earlier therapeutic eras, although SGLT2 inhibitors act through distinct mechanisms involving metabolic and renal pathways rather than neurohormonal blockade (20–22). These findings suggest that SGLT2 inhibitors address previously unmet pathophysiological targets in heart failure, including modulation of myocardial energy metabolism, reduction of congestion, and potential attenuation of myocardial fibrosis, thereby complementing established therapies (11,22).

In heart failure with preserved ejection fraction (HFpEF), where effective disease-modifying treatments have historically been limited, our meta-analysis supports evidence that SGLT2 inhibitors represent the first drug

class to demonstrate a clear and consistent reduction in heart failure hospitalizations (8,9). The magnitude of benefit in HFpEF approached a 20% relative risk reduction, with confidence intervals overlapping those observed in HFrEF trials, suggesting a broadly comparable treatment effect across the ejection fraction spectrum (23). These findings support consideration of SGLT2 inhibitors as foundational therapy in HFpEF, particularly in the context of limited alternative options. In line with the 2023 ESC Focused Update, dapagliflozin or empagliflozin is recommended in HFpEF to reduce the risk of heart failure hospitalization or cardiovascular death (Class I, Level A); importantly, across major HFpEF outcome trials, the observed composite benefit has been driven predominantly by reductions in heart failure hospitalizations, while cardiovascular mortality has generally remained neutral.

Our analysis also provides detailed subgroup insights that are consistent with existing evidence demonstrating benefits of SGLT2 inhibitors across diverse patient subsets and drug agents. Several systematic reviews and meta-analyses have confirmed similar efficacy in broad heart failure populations regardless of ejection fraction or diabetes status (24,25). Initial concerns that patients without diabetes might benefit less have not been borne out, as non-diabetic subgroups in randomized and pooled analyses demonstrate comparable reductions in heart failure events (26,27). This independence from glucose lowering corresponds with mechanistic data indicating that SGLT2 inhibitors exert pleiotropic physiological effects, including natriuresis and osmotic diuresis that reduce preload and afterload, improvements in hemodynamics, and potential enhancements in myocardial energetics (23,27,28).

In patients with HFpEF, large trials including EMPEROR-Preserved and DELIVER demonstrated reductions in composite cardiovascular outcomes and heart failure hospitalizations among those with ejection fractions of 50–60% or higher, indicating sustained benefit across the EF spectrum (23,29). Although attenuation of effect in very high EF strata (≥60%) was observed in individual trial subgroups, pooled analyses across HFpEF and HFmrEF cohorts continued to show event reduction in these patients, suggesting that SGLT2 inhibitors impact pathophysiological processes relevant to HFpEF, including volume handling, vascular load, and cardiorenal interplay.

A subgroup finding of relatively less benefit was observed in patients with advanced symptoms of heart failure (NYHA class III/IV). This pattern may relate to competing risks such as pump failure or arrhythmia, or to underrepresentation of the most frail patients in major trials. In contrast, observational and clinical trial evidence suggests that earlier initiation of SGLT2 inhibitors (either during hospitalization or soon after diagnosis) is feasible and associated with early outcome benefits, particularly reductions in rehospitalization and clinical improvement following acute decompensated heart failure. This was demonstrated in the SOLOIST-WHF trial, which showed significant reductions in worsening HF events and the composite of hospitalizations and cardiovascular death with sotagliflozin initiated during or shortly after hospitalization, as well as in the EMPULSE trial, where empagliflozin started during hospitalization resulted in clinically meaningful benefit over 90 days and was safe and well tolerated (30,31). Emerging meta-analyses and observational data further reinforce that initiating SGLT2 inhibitor therapy in the acute or early post-discharge phase is not associated with excess adverse events and is linked to reductions in rehospitalization rates (32).

Our integrated analysis of randomized controlled trials and observational data provides reassurance regarding the real-world effectiveness of SGLT2 inhibitors (33,34). While RCTs often enroll healthier or more adherent patients and exclude extremes of age and comorbidity, observational studies capture broader patient populations. The concordant findings, including similar or greater relative risk reductions in observational studies, strengthen external validity and support translation of trial benefits into routine clinical practice (24,33–35). At the same time, observational data highlight underuse, with registry studies showing that SGLT2 inhibitor uptake among eligible heart failure patients remains suboptimal, often below 20–25% (33–36). These findings underscore the importance of addressing therapeutic inertia to improve implementation.

Heterogeneity in the pooled analyses was generally low, indicating a class-wide effect. For HFpEF, moderate heterogeneity was observed, likely reflecting inclusion of smaller trials focused on surrogate endpoints; however, sensitivity analyses restricted to large outcome trials confirmed consistent results. No meaningful publication bias was detected.

Mechanistic considerations provide context for these clinical findings. SGLT2 inhibitors produce mild osmotic diuresis that contributes to early decongestion, as reflected by early separation of event curves. Unlike loop diuretics, they do not induce comparable neurohormonal activation and may reduce blood pressure and arterial stiffness. Additional mechanisms include enhanced myocardial fuel efficiency via increased ketone utilization, improvements in calcium handling, reductions in inflammatory signaling, and protection against cardiorenal dysfunction. In EMPEROR-Reduced, empagliflozin reduced the combined endpoint

of HF hospitalization or persistent decline in renal function by 50%, highlighting the integrated cardiorenal benefits of this drug class.

Our meta-analysis supports the incorporation of SGLT2 inhibitors as standard therapy for heart failure with reduced ejection fraction, alongside beta-blockers, ACE inhibitors or ARNIs, and MRAs. In HFpEF, they should now be considered first-line therapy given their consistent effect on heart failure hospitalizations. Initiation is straightforward, as SGLT2 inhibitors are administered once daily, are generally well tolerated, and do not require dose titration. Key considerations include baseline renal function and avoidance in patients at high risk for diabetic ketoacidosis.

Several potential concerns warrant clarification. Initial skepticism following early reports of reduced HF hospitalizations in EMPA-REG OUTCOME has been addressed by consistent findings across multiple independent trials, including in non-diabetic populations. Although HFpEF is a heterogeneous syndrome, the broad inclusion criteria of EMPEROR-Preserved and DELIVER support generalizability. While long-term data beyond five years remain limited, available evidence has not identified cumulative toxicity, and post-marketing surveillance continues. SGLT2 inhibitors provide incremental benefit regardless of background therapy, including ARNI and MRAs, and their early initiation may help prevent first and recurrent hospitalizations. Cost and adherence remain considerations, although cost-effectiveness analyses suggest favorable value due to reduced hospitalizations.

The strengths of this meta-analysis include its comprehensive evidence base, rigorous methodology, and focus on clinically meaningful outcomes. Limitations include reliance on observational studies that sometimes did not isolate heart failure populations and potential overlap among real-world datasets. We did not perform head-to-head comparisons between individual SGLT2 inhibitors, as the objective was to assess class effects.

could offer more contemporary and comprehensive insights into the impact of kidney dysfunction on MM outcomes.

CONCLUSION

SGLT2 inhibitors substantially improve outcomes in patients with heart failure, reducing heart failure hospitalizations and improving survival across the ejection fraction spectrum and irrespective of diabetes status. Evidence from both randomized controlled trials and real-world observational cohorts supports their role as cornerstone therapy in HFrEF and as an effective disease-modifying option in HFpEF and HFmrEF, with a favorable safety profile. Overall, our findings support a class effect of SGLT2 inhibitors in heart failure; however, agent- or dose-specific superiority cannot be inferred given the predominantly fixed-dose designs of heart failure trials and the absence of head-to-head comparisons. Wider implementation of SGLT2 inhibitor therapy has the potential to meaningfully reduce the global burden of heart failure and improve patient-centered outcomes.

DECLARATIONS

This study is a systematic review and meta-analysis of previously published randomized controlled trials and observational cohort studies. No new data were collected, and no individual patient-level data were accessed. All included studies had obtained approval from their respective institutional review boards or ethics committees, and were conducted in accordance with the principles of the Declaration of Helsinki and relevant regulatory standards.

Because this meta-analysis relied exclusively on aggregated data from published literature and publicly available sources, no additional ethical approval or informed consent was required for the present study. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251082754), ensuring transparency and adherence to predefined methodological standards.

The conduct and reporting of this meta-analysis followed the PRISMA 2020 guidelines. All efforts were made to ensure methodological rigor, minimize bias, and accurately represent the findings of the original studies. No ethical concerns related to patient safety, privacy, or data integrity were identified in the execution of this work.

Informed Consent Statement: Not applicable. This study did not involve direct interaction with human participants, nor did it include identifiable individual-level data.

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